771 Angioplasty Stents: Drugs for Prevention of Subacute Thrombosis

Wednesday, March 19, 1997, 8:30 a.m.–10:00 a.m.
Anaheim Hilton and Towers, Pacific D

771-1

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Ticlopidine Administration After Stent Placement: Frequency of Adverse Reactions

R.J. Russo, K.M. Stevens, S.L. Norman, D.A. Cloutier, P.S. Teirstein.
Scripps Clinic, La Jolla, CA, USA

During a 13-month period (January 1995 to January 1996), 682 patients underwent Palmaz-Schatz coronary stent placement at Scripps Clinic and were discharged on a variety of anticoagulation protocols, all of which included ticlopidine (500 mg/day) for 1 month. Discharge medications were: Ticlid (T) + aspirin (ASA) 325 mg/day in 385 (56.5%) pts; T + ASA + enoxaparin (E) 60 mg/day in 228 (33.4%) pts; T + ASA + warfarin (W) in 93 (13.6%) pts; and T + ASA + E + W in 18 (2.6%) pts. Patients were examined within 1 week of hospital discharge, a complete blood cell count was obtained at 2 weeks, and telephone follow-up was obtained at 1 month. *Results:* Adverse effects were experienced by 29 (4.25%) pts during the 1 month of ticlopidine administration and included rash in 13 (1.91%) pts, gastrointestinal (GI) distress in 8 (1.17%) pts, neutropenia (absolute neutrophil count [ANC] < 1500) in 5 (0.73%) pts, hives in 2 (0.29%) pts, and GI bleeding in 1 (0.15%) pt. In 12 (1.76%) pts who experienced an adverse effect, ticlopidine was tolerated for a full month after a reduction of dose to 250 mg/day. However, 17 (2.49%) pts required discontinuation of ticlopidine prior to 1 month due to a medication adverse effect. Indications for discontinuation were rash in 7 (1.03%) pts, GI distress in 6 (0.88%) pts, neutropenia (ANC < 1000) in 3 (0.44%) pts, and hives in 1 (0.15%) pt. The frequency of adverse effects was similar for all anticoagulation protocols (T + ASA, 4.25%; T + ASA + E, 4.0%; T + ASA + W, 2.22%; and T + ASA + E + W, 12.5%; p = ns). No patient experienced irreversible neutropenia. *Conclusion:* Ticlopidine therapy for 1 month after stent placement is associated with a low rate of adverse effects which require either reduction of dose or discontinuation of medication.

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771-2 Incidence of Neutropenia/Fatal Thrombocytopenia Associated With One Month of Ticlopidine Therapy Post Coronary Stenting

G. Szto, S. Lewis, K. Punamiya, S. Jung, R. Landin, M. Ball, Z. Hodes, D. Lips, J. Coverdale, T. Linnemeier. *Northside Cardiology, PC, Indiana Heart Institute, Indianapolis, IN, USA*

Objective: The reported incidence of neutropenia (NTP) (absolute neutrophil count [ANC] < 1200/ml) in patients (pts) on chronic ticlopidine (TIC) therapy for TIAs is 2.4%. The incidence of NTP or thrombocytopenia (TCP) with one month TIC therapy post coronary stenting has not been reported.

Methods: We prospectively studied complete blood counts (CBC) at 2, 4, and 6 weeks on 340 consecutive pts treated with coronary stenting from 4/95 to 6/96. A total of 542 stents (463 Palmaz-Schatz, 59 Gianturco-Roubin, 18 Multi-Link, 2 others) were placed in 353 lesions (mean 1.6 stents/pt). Mean age was 61 ± 11 years (males 70%). Adjunctive high pressure (>16 ATM) balloon dilatation was performed in all pts. A total of 98% (333/340) of pts were released on ASA, 100% on TIC, with sub-Q heparin used in high risk subsets.

Results: Neutropenia was detected in 4 pts (1.2%) with severe NTP (ANC < 450/ml) in 2 of these 4 pts (0.6%). TCP was detected in 2 pts (0.6%) with 1 (0.3%) death from cerebral hemorrhage. TIC was discontinued in 4/340 (1.2%) pts before one month because of a reduction in ANC without stent thrombosis. Subacute stent thrombosis occurred in 3/340 (0.9%) pts in the cohort as a whole.

Conclusion: The incidence of serious NTP is 1.2%, fatal TCP 0.3% of pts. A drop in ANC necessitating discontinuation of TIC occurred in 1.2% of pts. Further studies using TIC for shorter duration have been initiated. Meanwhile, pts receiving TIC for one month should continue to have serial monitoring of CBCs.

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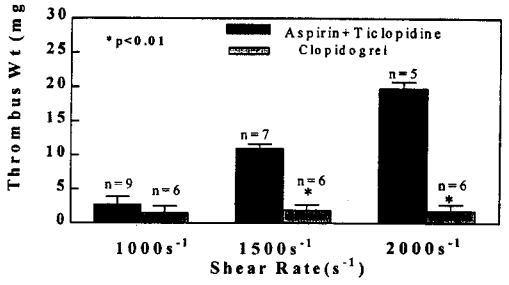
771-3 Clopidogrel, A Novel Platelet ADP-Receptor Antagonist Inhibits Aspirin and Ticlopidine-Resistant Stent Thrombosis

R. Makkar, N. Eigler, S. Kaul, H. Zeng, J.-M. Herbert [1], F. Litvack.
Cedars-Sinai Medical Center, Los Angeles, CA, USA, [1] *Sanofi Recherche, Toulouse, France*

Background: Combined aspirin (A) and ticlopidine (T) have been shown to reduce stent thrombosis (ST). However, the efficacy of this approach in small vessels under high-shear conditions is not known. *Methods and Results:* Pigs (n = 6, wt 23 ± 2 kg) were pretreated with ticlopidine (T) (250 mg po/d/3 days) and aspirin (A) (10 mg/kg iv). Unpolished nitinol stents (n = 39) were expanded to 2 mm diameter in a tubular perfusion chamber and interposed in an ex-vivo porcine arteriovenous shunt. Stents were exposed to flowing arterial blood at different shear rates (s^{-1}) for 20 minutes. Animals were then treated with clopidogrel (C) (5 mg/kg iv) and experiments were repeated. Shear was regulated by altering the blood flow. ST was quantified by measuring dry thrombus weight. ADP-induced (2.5 mM) platelet aggregation (PA) and bleeding time (BT) were estimated before and after C. C reduced PA by 45 ± 5% and prolonged BT from 4 ± 1 to 12 ± 2* minutes (p < 0.01).



Conclusions: Combined aspirin and ticlopidine do not inhibit acute thrombosis under conditions simulating high-risk stenting. Clopidogrel inhibits high-shear mediated stent thrombosis resistant to aspirin and ticlopidine under similar conditions.

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771-4 Reduction in Thrombogenicity of Cellulose Polymer-Coated Stents by Immobilisation of Platelet-Targeted Urokinase

R.K. Aggarwal, D.C. Ireland, M.A. Azrin [1], D.P. de Bono, A.H. Gershlick.
Department of Cardiology, University of Leicester, UK, [1] *University of Connecticut, Farmington, CT, USA*

We have previously targeted urokinase (UK) to platelets by chemical conjugation with anti rabbit platelet GP IIb/IIIa antibody (AZ1) and shown the enhanced platelet antiaggregatory effects of AZ1-UK conjugate compared with AZ1 antibody alone. This study aimed to evaluate the antithrombotic properties of AZ1-UK immobilised to cellulose polymer-coated stents (n = 22).

Methods: Antithrombotic effects were determined by implanting the stents into flow reduced, deeply injured iliac arteries of New Zealand White rabbits (n = 11). Each animal had a conjugate-immobilised stent in one vessel (Gr. I) and a base polymer control stent in the contralateral vessel (Gr. II). Arterial patency was determined after 2 hrs (n = 6 animals, acute group) and 28 days (n = 5 animals, chronic group). For the acute group, blood flow was measured continuously using perivascular flowprobes (Transonics, NY) and platelet adhesion determined using ^{111}Indium labelled autologous platelets. Total occlusion was defined as flow <0.5 ml/min for >10 min; cyclic flow variation (CFV) as return to flow >0.5 ml/min within 10 min. In the chronic

Gr.	Acute group				Chronic group
	[a]Platelets ($\times 10^7$)	[b]CFV freq: (hr^{-1})	[c]2 hr flow (% baseline)	[d]*n* occluded	[d]*n* occluded
I	16.7 ± 2.2	0	76.2 ± 10.3	0 of 6	1 of 5
II	35.4 ± 6.7	5.9 ± 2.2	16.4 ± 0.4	4 of 6	3 of 5

group, arterial occlusion was determined macroscopically after sacrifice.

Results are shown in the table. Compared with control vessels (Gr. II), arteries with conjugate-immobilised stents (Gr. I) had significantly less [a]platelet deposition (P = 0.0003), fewer episodes of [b]CFV (P = 0.0011), higher mean [c]2-hour flow (P = 0.0002) and significantly higher arterial patency [d]rates (P = 0.027).

Conclusion: Platelet-targeted urokinase passively immobilised to polymer-coated stents markedly reduces their thrombogenicity. Such devices may be particularly useful for anticoagulant-free stenting in small vessels or for bailout stenting and merit further evaluation.

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771-5 A New Biodegradable Polylactic Acid Coronary Stent-Coating, Releasing PEG-Hirudin and a Prostacycline Analog, Reduces Both Platelet Activation and Plasmatic Coagulation

G. Schmidmaier, A. Stemberger[1], E. Alt, M. Gawaz, F.-J. Neumann, A. Schömig. *I. Med. Klinik, Inst. for Exp. Surgery, Germany,* [1] *Technische Universität München, Germany*

Experience with coronary stenting has demonstrated that adhesion of plasma proteins to the metallic stent surface and platelet activation limit the implant effectiveness by means of acute and subacute thrombosis. We investigated a new stent coating of polylactic acid (PLA) carrier (25 kDa) containing 5% polyethylene glycol-hirudin and 1% prostacyclin analog (PGI2). *Methods:* 7 mm metallic stents (n = 48) were tested coated vs uncoated in a human stasis model with the non-anticoagulated blood of healthy volunteers. After 5 min thrombus weight, aPTT, markers of activated coagulation (thrombin-antithrombin-complexes TAT III and prothrombin fragments F1–2), collagen induced platelet aggregation and CD62p/CD41 expression were measured and scanning electronmicroscopy performed. *Results:* Uncoated stents were completely covered by a coagulation plug rich in fibrin and platelets. The coated stents were practically free from thrombotic material.

	Control without stent	Uncoated stent	Coated stent
Thrombus (mg)	–	2.02 ± 0.50**	0.02 ± 0.01
aPTT (sec)	29.87 ± 2.54	29.60 ± 2.35**	58.77 ± 9.24
TAT III (μmol/l)	5.92 ± 0.84	25.52 ± 4.45**	6.03 ± 1.13
F1–2 (nmol/l)	0.94 ± 0.07	2.14 ± 0.33**	0.99 ± 8.08
Platelet Aggreg. (%)	92.13 ± 4.24	90.82 ± 4.34**	10.53 ± 0.33
ΔCD62p	10.08 ± 0.66	12.63 ± 1.84*	11.73 ± 0.62
CD41a	146.56 ± 5.87	182.83 ± 4.78*	21.43 ± 3.22

*p < 0.05, **p < 0.001, coated vs uncoated stent

Conclusion: Our results show that PLA stent coating releasing PEG-hirudin and a prostacyclin analog has a significant effect on both platelet activation and plasmatic coagulation, thereby preventing stent induced thrombus formation.

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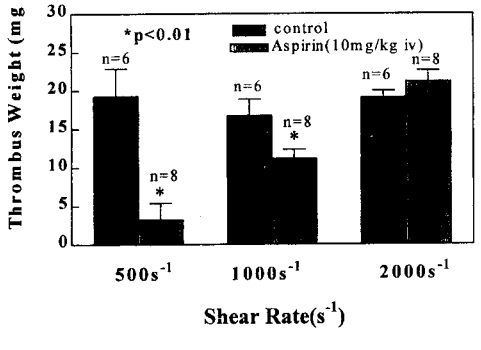
771-6 High-Shear Overrides the Antithrombotic Effects of Aspirin on Stent Thrombosis

R. Makkar, F. Litvack, S. Kaul, H. Zeng, N. Eigler. *Cedars-Sinai Medical Center, Los Angeles, CA, USA*

Shear at stent surfaces is affected by vessel size, blood flow, pre-existing thrombus and adequacy of stent deployment. We tested the efficacy of aspirin (10 or 20 mg/kg iv) at different blood shear rates. Unpolished nitinol stents (n = 48) were expanded to a diameter of 2 mm in a perfusion chamber and exposed to flowing arterial blood (n = 6 pigs) for 20 minutes in a porcine arteriovenous shunt model of stent thrombosis. Shear was regulated by altering the blood flow. Stent thrombosis was quantified by measuring dry thrombus weight. Data are mean ± sd. Arachidonic acid (540 mM)-induced platelet aggregation was inhibited by 48 ± 5% (p < 0.01) and bleeding time was mildly prolonged (360 ± 50 vs. 200 ± 30 secs; p = ns) with ASA 10 mg/kg. Higher doses of aspirin (20 mg/kg) similarly failed to inhibit ST (17 ± 2 vs 19 ± 1 mg for control, n = 6; p = ns) at the highest shear.



Conclusion: ASA inhibits stent thrombosis at low but not at high shear rates. In high-risk clinical situations characterized by high blood shear, ASA alone may not provide sufficient antiplatelet activity.

772 Interventional Cardiology: Acute Infarction and Unstable Angina

Wednesday, March 19, 1997, 8:30 a.m.–10:00 a.m.
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772-1 Predictors of Success and Major Complications for Primary PTCA in Acute Myocardial Infarction

E.D. Grassman, S.A. Johnson, R.J. Krone. *Loyola University Medical Center, Maywood, IL, USA, Washington University, St. Louis, MO, USA*

Primary angioplasty has recently been advocated as a safe and more effective treatment than thrombolytic therapy for acute myocardial infarction (AMI). The Society for Cardiac Angiography and Interventions (SCA&I) maintains a registry for diagnostic and interventional procedures. Primary angioplasty for AMI in the laboratories contributing to the registry was reviewed, and predictors of successful PTCA, in-hospital mortality, and emergency CABG were identified. 4,366 PTCA procedures were performed for AMI without prior thrombolytic therapy among 78,199 PTCA's (5.6%). Lab volume, age, sex, symptoms, intraaortic balloon pump (IABP) use, prior AMI, prior CABG, diabetes, hypertension, shock, moribund state, CHF, and prior PTCA of the same site were analyzed. The overall success rate was 91.5%, the in-hospital mortality rate was 2.5%, and the rate of emergency CABG was 3.4%. These are all similar to other published series. Higher PTCA volume and lower age were predictive of successful PTCA using multivariable logistic regression analysis, while an IABP in place, shock, and moribund state had negative predictive effects (p < 0.05). Unsuccessful PTCA, shock, and moribund state were predictive of in-hospital death (p < 0.05). Unsuccessful PTCA, the absence of hypertension, and absence of CHF were predictive of emergency CABG (p < 0.05).

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772-2 Nine-Year Outcome of Patients Undergoing Percutaneous Transluminal Coronary Angioplasty for Acute Myocardial Infarction: Report from the 1985–1986 NHLBI PTCA Registry

S.T. Lee, D.O. Williams, C.R. Cannan, K.E. Kip, S.F. Kelsey, K.M. Detre. *Rhode Island Hospital, Brown University, Providence, RI, USA*

Percutaneous transluminal coronary angioplasty (PTCA) is an effective means of achieving reperfusion in patients with acute myocardial infarction, but the long-term outcome of this therapy is unknown. Accordingly, we followed the clinical status of 1320 consecutive PTCA patients without history of MI (no MI), 619 patients with MI >30 days prior to PTCA (remote MI), 373 patients with MI 48 hours to 30 days prior to PTCA (recent MI), and 119 patients with MI within 48 hours of PTCA (acute MI). The in-hospital mortalities were no MI 0.8%, remote MI 1.0%, recent MI 1.9%, and acute MI 9.2% (p < 0.001). After a median of 9.0 years of follow-up, the risk of subsequent MI or bypass surgery did not differ by pre-procedural MI status with the exception that acute MI patients had less repeat PTCA (20.9%) than the other three groups (range 31.5%–42.7%, p < 0.01). Crude nine-year mortality, however, was highest in the acute MI patients (41.8%) when compared with recent MI (22.8%), remote MI (25.1%), and no MI patients (17.9%, p < 0.001). After adjusted multivariate analysis, MI within 48 hours of PTCA remained an independent predictor of nine-year mortality (relative risk = 1.75, p < 0.01).